REMARKS

Claims 18, 20-23, 25-28, 30-32, 34, and 35 have been rejected under 35 U.S.C. §102 as being anticipated by *The Effects of Three Non-Antibiotic, Antimicrobial Agents on the Surface Hydrophobicity of Certain Micro-Organisms Evaluated by Different Methods*; Journal of Applied Bacteriology 1991, 71, 218-227; by Jones *et al.* (hereinafter "Jones"). *All* of the claims (18-35) have been rejected under 35 U.S.C. §103(a) as being obvious over Jones in view of *A Comparative Study of the Microbial Anti-Adherence Capacities of Three Antimicrobial Agents*; Journal of Clinical Pharmacy and Therapeutics 1987, 12, 393-399; by Gorman *et al.* (hereinafter "Gorman").

Claims 18-35 are hereby cancelled. New claims 36-47 are to directed methods of using Taurolidine to reduce the adherence of *antibiotic-resistant* microorganisms to *epithelial cells*. The dependent claims include elements directed to specific strains of microorganisms (*enterococci*, *E. Faecalis*, *E. Faecium*, and *staphylococcus aureus*) having resistances to specific antibiotics (vancomycin-resistant, vancomycin-sensitive, vancomycin-intermediate susceptible, and methicillin-resistant) and to specific types of epithelial cells.

I. Jones Does Not Anticipate The Newly-Presented Claims

"An "anticipating" reference must describe all of the elements and limitations of the claim in a single reference, and enable one of skill in the field of the invention to make and use

the claimed invention." Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc., 2003 WL 22455179 (Fed. Cir. Oct. 30, 2003). The claims as newly-presented are directed to using Taurolidine to reduce the adherence of *antibiotic-resistant* microorganisms to epithelial cells. Accordingly, the claims as amended distinguish over Jones because Jones is silent with regard to the *antibiotic resistance* component of the instant claims. Insofar as Jones does not have this claim element Jones fails to teach each and every element of the claims, and therefore Jones does not anticipate any of the claims, as newly-presented.

Additionally, as will be discussed in the section that follows, Jones does not teach the use of Taurolidine as an anti-adherent as between microorganisms and epithelial cells (as claimed). Rather, Jones teaches Taurolidine as an agent for reducing the cell surface hydrophobicity (CHS) of microorganisms, without directly commending that property for use in reducing adherence to epithelial cells. Anticipation under 35 U.S.C. §102 requires that each and every element of the claimed invention be *identically* disclosed in a *single* prior art reference. Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 677 (Fed. Cir. 1988). That *single* prior art reference must disclose those elements *as they are arranged in the claim in question.* Lindemann Maschinenfabrik Gmbh v. American Hoist and Derrick Company, 730 F.2d 1452, 1458 (Fed. Cir. 1984). Since Jones teaches Taurolidine as a CHS-altering agent rather than as an anti-adherent as between microorganisms and epithelial cells, Jones fails to *identically* disclose these elements *as they are arranged in the claim in question.* Accordingly, Jones is a non-anticipating reference.

II. The Newly-Presented Claims Are Not Obvious Over J nes in View f Gorman

The Jones and Gorman combination of references fails to support a *prima facie* case of obviousness against the newly-presented claims. There are three basic requirements for the establishment of a *prima facie* case of obviousness. First, there must be some motivation or suggestion in the prior art reference itself, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine its teachings with that of another. Second, at the time the invention was made, the proposed combination / modification must be one that the artisan would have viewed as having a reasonable expectation of success. Lastly, the prior art reference(s), once modified or combined, must teach or suggest all the limitations of the claims. MPEP § 706.02(j).

Neither Jones nor Gorman contains any reference to *antibiotic resistance*, nor is there any indication that the strains studied in those references contained any such predispositions. Accordingly, there is no motivation or suggestion in either Jones or Gorman that would inspire the artisan of ordinary skill to use Taurolidine to reduce the adherence of *antibiotic-resistant* microorganisms to epithelial cells, as instantly claimed by new independent claim 36.

Furthermore, at the time the invention was made, one of ordinary skill in the art would **not** have viewed the claimed use of Taurolidine as an anti-adhesion agent against *antibiotic-resistant* microorganisms with a reasonable expectation of success. Significantly, Jones did *not* directly examine Taurolidine's ability to reduce the adherence of microoganisms to epithelial cells. Indeed, insofar as epithelial cells played absolutely no role in Jones' study, Jones did not even *indirectly* examine Taurolidine's ability to reduce the adherence of microoganisms to epithelial cells. Jones *actually* studied the effect of Taurolidine on the cell surface

hydrophobicity (CHS) of certain clinical microorganism strains, *apart* from epithelial cells. (Jones, Abstract). Jones noted that the importance of CSH for the adherence to epithelial cells has been suggested for *Streptococcus salivarius*, *Streptococcus sanguis*, *Actinomyces naeslundii*, and *E. coli*. (Jones page 218, last paragraph). Yet, Jones admonishes that this theory is open to debate:

> "However, there is still some debate concerning the relative importance of cell surface hydrophobicity (CHS), with **some authors relegating the overall role of hydrophobic interactions to a contributing factor in the adherence process** (Parker & Munn 1984) and **others reporting no correlation** (Bandin *et al.* 1989)."

Accordingly, Jones teaches the artisan nothing with regard to Taurolidine's ability to *reduce adherence*, and at best Jones *equivocates* on the importance of the Jones-studied CHS with regard to *its* (CHS's) relation to *reducing adherence*. The artisan having studied Jones would not attribute any anti-adherence properties to Taurolidine, especially in view of Jones' *own* suggestion that the use of Taurolidine to *increase* the microorganism's *hydrophobicity* (and thereby, theoretically, *reduce* its adherence) is unpredictable:

> "The effect of taurolidine treatment of these organisms resulted in an alteration in the cell surface characteristic to one of greater hydrophobicity, **with the exception of *Staph. epidermis* (the most hydrophilic organism) where the opposite effect was noted**." (Jones page 220, col. 2).

That Jones' teachings do not permit of predictable prognostication with regard to the studied effects of taurolidine on CHS, renders Jones relevance with regard to anti-adherence even less instructive for the artisan of ordinary skill.

While Gorman *does* teach Taurolidine as an anti-adherent agent as between microorganisms and epithelial cells, there is no indication in Gorman that the *Candida albicans* or *Escherichia coli* therein-studied were *antibiotic-resistant*, as herein-claimed. Accordingly, at the time the invention was made one of ordinary skill in the art would **not** have viewed the

claimed use of Taurolidine to reduce the adherence of *antibiotic-resistant* microorganisms to epithelial cells with a reasonable expectation of success.

This is further evidenced by *Activities of Taurolidine In Vitro and in Experimental Enterococcal Endocarditis*, by C. Torres-Viera *et al.*, Antimicrobial Agents and Chemotherapy, June 2000, p. 1720-1724, Vol. 44, No. 6 (hereinafter "Torres-Viera ") **Exhibit A**. As Torres-Viera explains it is not possible to generalize as to the effectiveness of taurolidine *in treating infection* caused by microorganisms, which infection under the Jones / Gorman theories is adherence-dependent. The Torres-Viera reference—authored by doctors at Beth Israel Medical Center and Harvard Medical School regarding research conducted *circa* the instant application's filing date—clearly suggests that taurolidine does not necessarily have a predictable spectrum of activity. In two separate rat models (Sprague-Dawley and Wistar) Torres-Viera found that taurolidine was *ineffective* against infections due to ***E. faecium*** (claimed in dependent claim 40). Torres-Viera also found that taurolidine was equally useless in infected rat models against **vancomycin-resistant *enterococci*** and **methicillin-resistant *Staphyloccocus aureus*** (claimed in dependent claims 37-40 and 42 respectively):

> "To determine whether taurolidine activity could be demonstrated in vivo in our experimental model, we employed the maximum doses which could be physically administered with combined i.v. plus i.p dosing. Even with such doses, **we were unable to show activity *in vivo* against either test organism in this model**." (Torres-Viera page 4 of 6, emphasis added).

And, Torres-Viera concludes that taurolidine might *not* be able to achieve the necessary minimum inhibitory concentrations to be effective against some strains:

> **"Because peak concentrations of taurolidine and its metabolites determined to date in the plasma of humans do not appear to reach the MICs [Minimum Inhibitory Concentrations] against many of the strains of concern, it seems doubtful that this drug would have a significant role in the systemic therapy of established infecti ns."** (Torres-Viera, page 4 of 6, emphasis added).

Accordingly, Torres-Viera's disclosure of the failings of taurolidine *in vivo*, against several of the *claimed* microorganisms also having the *claimed* antibiotic resistances, seriously underscores the degree to which the artisan would **not** have reasonably expected the *claimed* use of Taurolidine to be an effective anti-adhesion agent, at the time the invention was made.

Surely, the artisan having studied the Jones and Gorman references, bearing in mind the debated theory that *infection* is adherence-dependent, would have been lead away from the instant claims in view of Torres-Viera's teaching that taurolidine performed unfavorably *in vivo* in the *infected* rat. These of Torres-Viera's observations could only lead the Jones-instructed and / or Gorman-instructed artisan to believe that taurolidine did **not** have anti-adherence properties, as even "the maximum doses which could be physically administered with combined i.v. plus i.p dosing" showed **no** activity against *antibiotic-resistant* strains, as claimed. For each of the foregoing reasons Jones and Gorman fail to support a *prima facie* case of obviousness, and the instant claims are patentable over those references.

Additionally, Jones examined Taurolidine only against isolates of *Escherichia coli*, *Staphylococcus saprophyticus*, *Staphylococcus epidermis*, and *Candida albicans*. Gorman is similarly limited in scope, having examined Taurolidine only against *Candida albicans* and *Escherichia coli*. In contrast, newly-presented dependent claims 37-42, in addition to reciting varying resistances to specific antibiotics (vancomycin and methicillin), are directed to *enterococci* and *Staphylococcus aureus*, neither of which are mentioned by Jones or Gorman.

In view of the foregoing, Applicants submit that newly-presented independent claim 36 is patentable in view of the cited references. The remaining claims, each of which depend from claim 36, are directed to further aspects of the invention in combination with those of claim 36,

and they are therefore similarly patentable in view of the cited references.

In further view of the foregoing, Applicants submit that the application is in condition for allowance, and they therefore request its prompt passage to issue.

It is believed that no fee is due. However, if any fee is due it should be charged to Deposit Account No.: 03-0678.

CERTIFICATE OF MAILING

Deposit Date: January 28, 2004

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1/28/04

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#208615 v1 - response to non-final rejection

Respectfully submitted,

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